UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte BERNHARD HAUER, ROLF D. SCHMID, MARKUS ENZELBERGER, and STEPHAN MINNING

Appeal No. 2005-2596
Application No. 09/674,962

ON BRIEF

ELLIS, SCHEINER and MILLS, Administrative Patent Judges.

ELLIS, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal pursuant to 35 U.S.C. § 134 from the examiner's final rejection of claims 1-4. According to the examiner, claim 6 has been allowed and claim 5 "would be allowable if rewritten in independent form." Answer, p. 2. Claims 7-18 have been withdrawn from consideration pursuant to 37 CFR § 1.142(b).

As a preliminary matter, we note the appellants' statement on page 3 of the Brief that the claims "have not been argued separately." Accordingly, for purposes of this appeal, we will consider the issues as they apply to claim 1 which is representative of the claims on appeal. Said claim reads as follows:

1. A peptide fragment having the general sequence

His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys (SEQ ID NO:1),

where the variables X^1 to X^6 in the sequence have the following meanings:

X^1 = an amino acid selected from the group consisting of Ala, Val, Phe, Ser, Met, Trp, Tyr, Asn, Asp or Lys and the variables X^2 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^2 = an amino acid selected from the group consisting of Val, Ile, Phe, Pro, Trp, Tyr, Gln, Glu or Arg and the variables X^1, X^3 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^3 = an amino acid selected from the group consisting of Gly, Ile, Thr, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and the variables X^1, X^2 X^4 to X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^4 = an amino acid selected from the group consisting of Val, Phe, Pro, Cys, Met, Trp, Asn, Glu, Arg or His and the variables X^1 to X^3, X^5, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^5 = an amino acid selected from the group consisting of Gly, Ser, Cys, Met, Trp, Asn, Glu, Lys or Arg and the variables X^1 to X^4, X^6 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His or

X^6 = an amino acid selected from the group consisting of Phe, Pro, Ser, Cys, Trp, Tyr or Gln and the variables X^1 to X^5 an amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Phe, Pro, Ser, Thr, Cys, Met, Trp, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His and

where at least one of the variables X^1 to X^6 in the sequence is, independently [sic, independent] of one another, Gln or Asn.

The claims stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Volz[1] in view of Guerinot[2] and Haymore.[3]

We have carefully considered the respective positions of both the appellants and the examiner and find ourselves in substantial agreement with that of the examiner. Accordingly, we affirm.

Discussion

As indicated by claim 1, above, the present invention is directed to a peptide fragment comprising a histidine-X-histidine (his or H) and a cysteine-X-X-cysteine (cys or C) motif, wherein "X" represents another amino acid. According to the specification, polypeptides or fusion proteins which contain the peptide fragment of claim 1 "can be purified easily, at low cost" [p. 9, lines 15-17] by bringing said polypeptides in "contact with immobilized metal ions so that an affinity linkage between the [polypeptide] and the metal ions can form [page 10, lines 33-35]."

It is well established that the examiner has the initial burden under § 103 to establish a prima facie case of obviousness. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); In re Piasecki, 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-88 (Fed. Cir. 1984). To that end, it is the examiner's responsibility to show that some objective teachings or suggestions in the applied prior art, or knowledge generally available [in the art] would have led one of ordinary skill in the art

[1] Volz et al. (Volz), "Molecular Characterization of Metal-Binding Polypeptide Domains by Electrospray Ionization Mass Spectrometry and Metal Chelate Affinity Chromotagraphy," Journal of Chromatography A, Vol. 800, pp. 29-37 (1998).
[2] Guerinot et al. (Guerinot), U.S. Patent No. 5,846,821, issued December 8, 1998.
[3] Haymore et al. (Haymore), EPA 409 814, published January 23, 1991.

to combine the references to arrive at the claimed invention. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). This the examiner has done.

Volz discloses that peptides containing H-X-H sequences bind with high affinity to nickel (Ni^{2+}) and copper (Cu^{2+}) ions. Volz, p. 29, the abstract. Volz further discloses that C-X-X-C sequences, which are present in zinc finger proteins, bind to Cu^{2+}, Zn^{2+} and Ni^{2+}. Id., p. 29, col. 1. Volz still further discloses that polypeptides which contain an H-X-H-X-X-X-C-X-X-C motif bind to Ni^{2+} and Cu^{2+}. Id., p. 32, col. 2, last complete sentence; Figure 2; p. 37, col. 1. The examiner points out that the peptide fragment disclosed by Volz is identical the peptide fragment set forth in claim 1 except the prior art fragment has a leucine (Leu) residue at position 9 (X^3 of the claimed general sequence), rather than an isoleucine (Ile). Answer, p. 4. To establish that this minor difference in amino acid sequence would have been obvious to one of ordinary skill in the art, the examiner relies on Guerinot's disclosure that Leu and Ile are conservative amino acids. Thus, the examiner argues that "one can replace the other without the loss of peptide activity." Answer, p. 5. The examiner further argues that Haymore discloses that the intervening amino acids between the His residues in metal binding peptides are not important. Id. (relying on Haymore, p. 4, lines 10-13). The examiner concludes that "it would have been obvious to one having ordinary skill in the art at the time the invention was made to replace Leu in the peptide fragment of Volz with a homologous amino acid, Ile, as taught by Geurinot" especially since Haymore discloses that the "intervening residues between the His and Cys metal binding residues are [] unimportant in the binding of peptide fragments to metals." Id.

In response, the appellants argue that there is no motivation to combine the teachings of Volz, Geurinot and Haymore. Brief, p. 4. We disagree.

First, we find that the appellants do not contest the examiner's finding that Leu and Ile are conservative amino acids which can substitute for one another. Answer, p. 5.[4] In other words, Leu and Ile are functional equivalents. We point out that our appellate reviewing court has held on several occasions that "[s]tructural relationships often provide the requisite motivation to modify known compounds to obtain new compounds." In re Mayne, 104 F.3d 1339, 1343, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997) citing In re Deuel, 51 F.3d 1557, 1558, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995); see also, In re Dillon, 919 F.2d 688, 693 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)("structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness"). Thus, given the established structural relationship between Leu and Ile, and the teachings of Volz as to peptide fragment having the sequence His-X^1-His-X^2-X^3-X^4-Cys-X^5-X^6-Cys, wherein the only difference between the prior art peptide fragment and the peptide fragment of representative claim 1 is a Ile residue at position x^3 instead of a Leu residue, we agree with the examiner that it would have been obvious to one of

[4] We point out that Geurinot (col. 14, lines 18-21), also discloses that "[a] 'conservative amino acid substitution' is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain." Geurinot further discloses that leucine and isoleucine have non-polar side chains. Lines 26-27. Thus, it reasonably follows that leucine and isoleucine are conservative amino acids and are members of the same family (of non-polar amino acids).

ordinary skill in the art to construct a peptide fragment having the claimed conservative amino acid substitution (i.e., a peptide fragment wherein X^3 is a Leu residue).

Second, this is not a case of first impression. The Court has previously agreed with the Board of Patent Appeals and Interferences that Leu and Ile are functional equivalents. In in re Mayne, the facts involved an invention which had a Leu residue at a particular position in a protein; whereas, the prior art protein contained an Ile residue at said position. The Court stated that "Leu is an isomer of Ile—an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains, also known as R-groups, of Leu and Ile have the same number of hydrogen and carbon atoms. Both are nonpolar, hydrophobic amino acids. The structure of Leu and Ile alone suggest their functional equivalency."

In view of the known structural relationship between Leu and Ile, we find that the teachings of Volz alone would have suggested the claimed invention to one of ordinary skill in the art. Guerinot merely provides evidence of the correctness of the examiner's position that these two amino acids are functional equivalents. We further find that the teachings of Haymore are cumulative in that like Volz the patent application discloses that it is the spacing or distance between the two histidine and two cysteine residues which is important and not the amino acid composition itself.

We find the appellants' arguments that (i) Volz does not teach a method of using the H-X-H-X-X-X-C-X-X-C motif to purify other proteins; and (ii) the claimed amino acid sequences "bind to immobilized metal ions at least 1.5 times more strongly than" that which is taught by Volz, to be misdirected. Brief, p. 5. First, representative claim 1 is directed to a composition and not to a method of use. Second, the claim does not require any specific level of binding to a metal ion. Thus, these arguments do not address a limitation present in the claims.

To the extent that the appellants might have intended to argue that the ability of the claimed protein to bind a metal ion 1.5 times more strongly than the prior art protein (of Volz) is evidence of an unexpected result, we agree with the examiner that, at best, the specification only discloses one clone, M13, which binds at that affinity. Answer p. 7 (relying on page 20, lines 42-44). Thus, this argument is not commensurate in scope with the invention set forth in representative claim 1. Moreover, as pointed out by the examiner, for a showing of unexpected results to be probative evidence of nonobviousness, the appellants must not only establish that there is a difference between the results obtained for the claimed invention and those of the prior art, but they must also demonstrate that the difference obtained is significant and would not have been expected by a person having ordinary skill at the time the invention was made. In re Freeman, 474 F.2d 1318, 1324, 177 USPQ 139, 143 (CCPA 1973); In re D'Ancicco, 439 F.2d 1244, 1248, 169 USPQ 303, 306 (CCPA 1971). This the appellants did not do.

Accordingly, the rejection is affirmed.

Another Issue

Upon return of the application to the corps, the examiner may wish to reconsider whether claims 5 and 6 are patentable over the teachings of the applied prior art. We point out that in the Answer (page 9), the examiner argues that "Volz positively teaches the essential or critical residues for metal ion binding are the His and Cys residues." In this regard, we find that Volz refers to the different metal ion binding regions as "motifs." For example, Volz describes the correspondent peptide as containing a H-X-H-X-X-X-C-X-X-C motif. See, e.g., the abstract. Thus, Volz suggests, and Haymore confirms (p. 4, lines 10-13), that the intervening amino acids denominated as "X" are not critical to the metal binding activity of the peptide. In addition, Haymore states that the intervening residues are not important. Therefore, the examiner should consider whether the teachings of Volz and Haymore would have suggested that any naturally-occuring amino acid could be used in the H-X-H-X-X-X-C-X-X-C motif. This would include the amino acids recited in claims 5 and 6.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Joan Ellis)
Administrative Patent Judge)
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)
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